Use of Extended Criteria Livers Decreases Wait Time for Liver Transplantation Without Adversely Impacting Posttransplant Survival

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Introduction: The use of extended criteria donors (ECDs) could minimize shortage of suitable donor livers for transplantation. In 3 years, the aggressive use of ECD livers has reduced the wait list at our center from 257 to 30 patients with a median wait time of 18 days without using living donors. This study compares the graft/patient survival from standard (SD) and ECD for our transplant population between 2001 and 2005.

Methods: Records of all adult liver transplant recipients over 4 years were reviewed (n = 571). ECD criteria included: age >59 years, BMI >34.9, maximum AST/ALT >500, maximum bilirubin >2.0, peak serum sodium >170, HBV/HCV/HTLV reactive, donation after cardiac death, cold ischemia time >12 hours, ICU stay >5 days, 3 or more pressors simultaneously, extensive alcohol abuse, cancer history (nonskin), active meningitis/bacteremia, or significant donor liver trauma. Outcomes included graft and patient survival at 90 days, 1 year, and 2 years.

Results: Sixty-eight percent of recipients (n = 388) received ECD livers. Primary factors accounting for ECD-liver status included: elevated liver function tests (20%), hypernatremia (12.6%), and extensive alcohol abuse (11.4%). Graft survival was (SD, ECD): 90-day 91%, 88%; 1-year 84%, 80%; 2-year 78%, 77%; patient survival was: 90-day 93%, 90%; 1-year 87%, 82%; 2-year 83%, 79%. Kaplan-Meier survival analysis failed to demonstrate an overall difference in graft or patient survival at any time point. Only donor age >60 years was associated with decreased graft and patient survival.

Conclusions: Liver grafts from ECD can be used to dramatically reduce wait list time with outcomes comparable to those for SD without resorting to living donor liver transplantation.

(*Ann Surg* 2006;244: 439–450)

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ISSN: 0003-4932/06/24403-0439
DOI: 10.1097/01.sla.0000234896.18207.fa

Liver transplantation is the therapy for choice for most forms of end-stage liver disease.[1] The United Network for Organ Sharing (UNOS) liver transplant wait list now exceeds 17,000 patients, and each year there are less than 6500 cadaveric liver transplants performed in the United States. The shortage of suitable donor livers is the most pressing problem facing liver transplantation today. Live donor and split liver transplantation have been used to ease the donor shortage, but they have failed to make a significant dent in the number of patients on the wait list. Live donor and split liver transplantation have ethical issues and technical complexities that make them less than ideal ways to expand the donor pool.[2–4] Liberalization of acceptance criteria is another means of expanding the available pool of donors so that more people on the wait list can benefit from life-saving liver transplants. Grafts used based upon liberalization of acceptance criteria have been called extended criteria donors (ECD). The use of extended criteria liver donors is limited by surgeon concern for the potential of doing harm to the patient if the liver has primary nonfunction (PNF) or initial poor function.[5] The possibility of using ECD livers has led some to suggest that there will be a need for a special consent that patients must sign to agree to receive an ECD liver.[6] The problem with this suggestion is that there are no uniform criteria defining ECD livers. Over the years, donor-related factors have been identified that may result in diminished graft and patient survival following liver transplantation. These factors include prolonged cold ischemic time, donor age, female sex, high serum sodium (Na+ >155), positive serologies for HBV/HCV/HTLV-1 and -2, donor steatosis, elevated transaminases, elevated bilirubin, prolonged down time, and donation after cardiac death.[7–13]

Liver transplantation is a complex operation performed on patients with a myriad of confounding variables that makes determination of graft failure and patient death a very difficult task. As a result, little is known about which donor livers will not work; rather, there is an extensive network of information regarding which livers are safely in the realm of non-ECD livers.

The results in this manuscript examine the routine use of ECD livers and its impact on wait list transplant rate, and graft as well as patient survival at our center. These results begin to

examine the definition of ECD livers. If the clinical outcome using these grafts is not different from universally accepted standard donors, the definition of ECD livers should be changed.

METHODS

The medical records of all orthotopic liver transplants performed between July 1, 2001 and June 30, 2005 were reviewed. Extracted data came from the comprehensive transplant recipient registry at our center, individual written and electronic medical records, and the original donor medical history. Recipient inclusion criteria included all transplant recipients age 18 and older receiving either an isolated orthotopic liver transplant or a simultaneous cadaveric liver and kidney transplant. Graft and patient survival data were collected from the transplant database at our center. In patients receiving retransplantation within 30 days of the original transplant, the analysis included only patient and graft survival data for the first transplant. This study was reviewed and approved by the institutional review board of the Indiana University School of Medicine.

Liver donor demographic and clinical data were reviewed from the original donor charts as recorded by the on-site organ procurement organization representative. A literature review was undertaken prior to the data collection phase of this study to determine all donor factors that have been previously cited as potentially impacting liver transplant outcome. ECD criteria for this analysis included: age >59 years, body mass index (BMI) >34.9 kg/m^2, maximum AST or ALT >500, maximum bilirubin >2.0, peak serum sodium >170, HBV/HCV/HTLV reactive, non–heart-beating donor, cold ischemia time >12 hours, ICU stay >5 days, 3 or more pressors simultaneously, extensive alcohol abuse, cancer history (nonskin), active meningitis/bacteremia, or significant donor liver trauma (Table 1). Percent steatosis was not included in our donor data set. Although an estimation of steatosis was included in the donor charts, there was no mechanism for validation of these estimates, and we found them to be unreliable. We do not routinely require pretransplant donor liver biopsy. The ECD criteria in Table 1 are comparable to, or more restrictive than, those criteria used in similar studies of marginal donors in liver transplantation. These restrictive parameters were used in the analysis in an attempt to accentuate any potential effect of these factors on transplant outcome. As previously stated, these factors have not been validated as criteria for an extended criteria liver donor given the lack of consensus on the definition. For this cohort, there were no ABO mismatches. While patients receiving combined liver and kidney transplantation were included in the analysis, those receiving other multivisceral transplants were excluded.

All recipients were listed for transplantation according to standard procedures and protocols as established by UNOS. Median model for end-stage liver disease (MELD) score at transplant was 17 (range, 6–40). The low median MELD score at our center is a consequence of our high volume and short wait time. Donor livers were recovered using standard procurement techniques including aortic and portal vein flushing and cold storage. The median cold ischemia time was 7 hours. Eighty-two percent of the transplants were performed using a piggyback hepatectomy approach. The protocol at our program is to close skin only and return for fascial closure on postoperative days 3 to 7 to minimize compartment pressures in the immediate reperfusion period. Posttransplant immunosuppression included induction with rabbit antithymocyte globulin (total dose, 6 mg/kg) with a rapid steroid taper of 3 doses of solumedrol (500, 250, and 120 mg) and maintenance with tacrolimus monotherapy. Approximately one half of the recipients received a single dose of rituximab on postoperative day 3 as part of the induction protocol. The overall rate of rejection for all recipients is less than 10%. Mild rejection is treated at our center with an increase in baseline immunosuppression. More severe rejection is treated with solumedrol 500 mg daily for 3 days.

TABLE 1. No. (%) of Donors Within Specified Parameters for Each Aspect of Extended Donor Criteria for All Recipients (n = 571)

	No. (%)
Extended criteria donors	388/571 (68.0)
Age ≥60 yr	60 (10.5)
BMI ≥35 kg/m^2	51 (8.9)
Maximum serum Na+ ≥170 mEq/L	72 (12.6)
Maximum total bilirubin ≥2.0 mg/dL	71 (12.4)
Maximum AST ≥500 μ/L	47 (8.2)
Maximum ALT ≥500 μ/L	27 (4.7)
Elevated LFTs (Any of following 3: AST/ALT/total bilirubin)	117 (20.5)
Serology (HBV or HCV or HTLV)	55 (9.6)
Non-heart beating donor	16 (2.8)
Cold ischemia time >12 hours	20 (3.5)
More than 2 pressors at any time	58 (10.2)
ICU stay greater than 5 days	53 (9.3)
EtOH use >30 g/day for 10 years or more	65 (11.4)
Current central nervous system tumor	14 (2.5)
Current meningitis	2 (0.4)
Any history of non-skin cancer	13 (2.3)
Significant liver trauma (>grade I injury)	15 (2.6)

Primary transplant outcomes included graft and patient survival at 3 months, 1 year, and 2 years. Recipients of ECD and standard donors were compared using a χ^2 test with significance being $P < 0.05$. All occurrences of graft loss or patient death were included in the final analysis regardless of etiology, comorbidities, or timing. Specifically, there were no exclusions for perioperative mortality or graft loss or for non–liver-related deaths. Although many perioperative deaths are technical in nature, the possibility of the ECD-liver contributing to an early demise necessitates the inclusion of all recipients. Subgroup analysis was performed using χ^2 testing to individually identify those ECD criteria associated with graft or patient loss. Recipients were compared by donor status (ECD vs. standard donor) using a Kaplan-Meier survival curve with statistical testing by the log rank and χ^2 tests. Statistical testing was performed on SPSS software (SPSS 13.0 for Windows, SPSS Inc., 2004).

RESULTS

Recipient and Donor Demographics

During the 4-year study period, 651 cadaveric liver transplants were performed, of which 571 met inclusion criteria for this analysis. The primary reason for exclusion was recipients who were younger than the age of 18 years. There were 388 transplant recipients (68.0%) who received livers from extended criteria donors and 183 (32.0%) who received livers from standard donors (Table 1). Comparison of recipient and donor demographics is listed in Table 2. Sixty-six percent of recipients and 56% of donors were male with mean ages being 52 and 40 years, respectively. The most common causes of death for

TABLE 2. Liver Recipient and Donor Demographics With a Statistical Comparison of the Demographic for Standard (SD) and Extended Criteria Donors (ECD)

TOTAL	ALL	Standard	ECD	*P** (SD vs. ECD)
Recipient gender				NS
Male	378/571 (66.2%)	119/183 (65.0%)	259/388 (68.9%)	
Recipient race				NS
White	518/571 (90.7%)	168/183 (91.8%)	360/388 (90.2%)	
Other	53/571 (9.3%)	15/183 (8.2%)	38/388 (9.8%)	
Recipient age (years)				0.002
Mean	51.9	50	52.6	
Median	52	50	52	
Range	18 to 72	17 to 72	18 to 72	
Recipient BMI				NS
Mean	28.1	27.8	28.2	
Median	28	28	28	
Range	15.6 to 42.5	15.6 to 39.6	16.3 to 42.5	
Recipient/donor AED				NS
A	230/571 (40.3%)	78/183 (42.6%)	152/388 (39.2%)	
B	57/571 (10.0%)	17/183 (9.3%)	40/388 (10.3%)	
AB	10/571 (1.8%)	1/183 (0.5%)	9/388 (2.3%)	
O	274/571 (48.0%)	87/183 (47.5%)	187/388 (48.2%)	
Recipient MELD at transplant				0.02
Mean	18.3	19.1	17.9	
Median	17	18	16	
Range	6 to 48	6 to 43	6 to 48	
Retransplant	23 (4.0%)	14/183 (7.7%)	8/388 (2.3%)	<0.01
Donor gender				NS
Male	318/571 (55.7%)	109/183 (59.6%)	209/388 (53.9%)	
Donor age				<0.01
Mean	40.2	36.8	41.8	
Median	42	38	43	
Range	6 to 81	9 to 59	6 to 81	
Donor race				NS
White	471/571 (82.5%)	161/183 (88.0%)	310/388 (79.9%)	
Black	77/571 (13.5%)	18/183 (9.8%)	59/388 (15.2%)	
Other	23/571 (4.0%)	4/183 (2.2%)	19/388 (4.9%)	
Donor cause of death				0.06
Stroke	250/571 (43.8%)	81/183 (88.0%)	169/388 (43.6%)	
Trauma	206/571 (36.1%)	75/183 (41.0%)	131/388 (33.8%)	
Other	115/571 (20.1%)	27/183 (14.8%)	88/388 (22.7%)	
Total cold ischemia time (hours)				NS
Mean	7.5	7.2	7.6	
Median	7	7	7	
Range	3 to 20	3 to 12	3 to 20	
Total warm ischemia time (minutes)				0.02
Mean	48.0	49	47.6	
Median	43	46	40	
Range	14 to 203	16 to 135	14 to 203	

*Categorical variables compared using χ^2 test. Continuous variables compared using median test.
P value <0.05 considered significant for both tests. NS, non-significant.

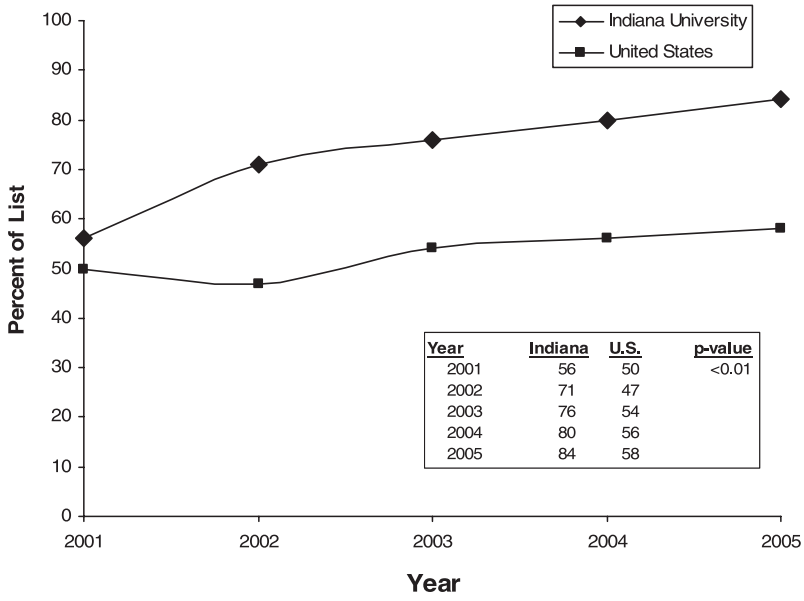

FIGURE 1. Comparison of wait list removal for transplantation for Indiana University and United States overall (P value < 0.01 for comparison of groups).

donors were cerebral vascular (44%) and trauma (36%). The most frequently cited criteria for classification as an ECD liver included: elevated liver function tests (20.5%), elevated serum sodium (12.6%), and history of alcohol abuse (11.4%). The standard and ECD donors groups did not differ significantly in recipient gender, race, BMI, or ABO type. The ECD livers were more likely to be given to an older recipient (50 vs. 52 years, $P = 0.002$) and to a recipient with a lower MELD score (18 vs. 16, $P = 0.02$). The 2 groups did not differ in donor gender, race, cause of death, or in total cold ischemia time. The ECD donors had a higher median age (38 vs. 43 years, $P < 0.01$) and a shorter warm ischemia time (46 vs. 40 minutes, $P = 0.02$) and were more likely to have died of a cause other than stroke or trauma (15% vs. 23%, $P = 0.06$). ECD donors were used less frequently in late retransplants (9 of 388 vs. 14 of 183, $P < 0.01$).

Impact of ECD Utilization on Wait List Activity

The liberalization of acceptance criteria resulted in an increase in the percentage of wait list removals for transplantation that was significant ($P < 0.01$) when compared with the national average (Fig. 1). There was a decrease in the percentage of removals for death or too sick to transplant that was also significant ($P = 0.04$) when compared with the national average (Fig. 2). The rate of transplants per patient year on the wait list is a good tool to monitor a program's transplant activity and is calculated yearly by the Scientific Registry of Transplant Recipients. The impact of the utilization of ECD livers has clearly impacted the transplant rate at Indiana University that is significantly higher than the national average (Fig. 3).

Graft and Recipient Survival

Graft and patient survival for standard and ECD donors are displayed in Table 3. There was no significant difference between the overall ECD and standard donor groups regarding graft or patient survival at any measured time point. Kaplan-Meier survival curves for graft and patient survival are shown in Figure 4. Subgroup analysis was performed to determine which of the marginal donor criteria were predic-

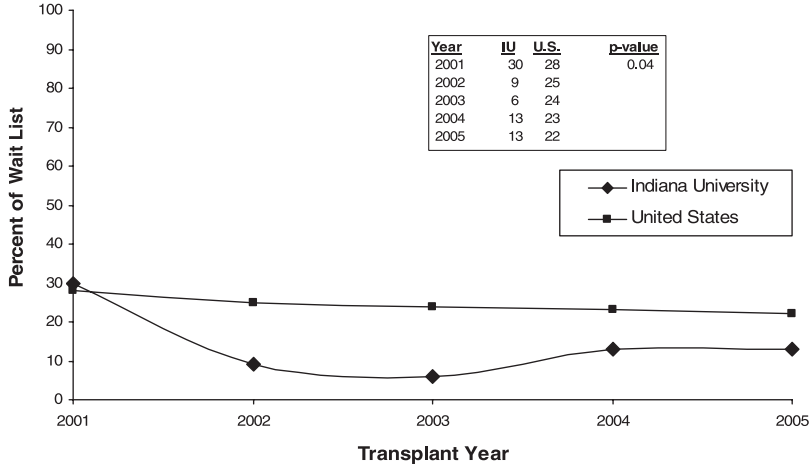

FIGURE 2. Wait list removal for patient dying or being too sick to transplant: Indiana University and United States overall ($P < 0.05$ for comparison of groups).

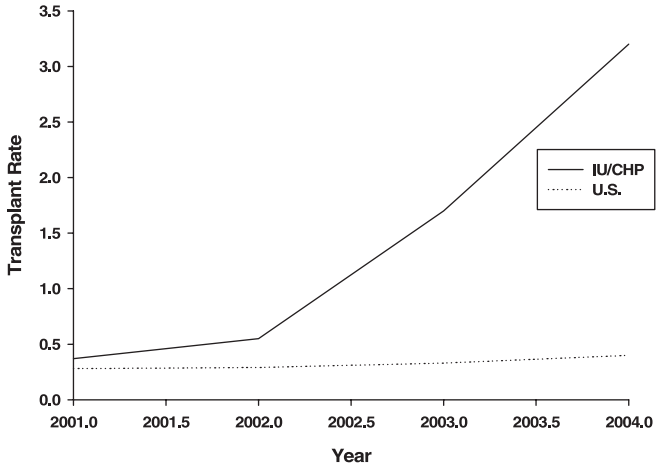

FIGURE 3. Comparison of Indiana University/Clarian Health Partners (IU/CHP) and U.S. average for transplant rate per patient year of wait list time.

tive of 3-month, 1-year, and 2-year survival. At 3 months, those subgroups with worse survival than standard donors included older donors ($P < 0.05$) and those with a cold ischemia time greater than 12 hours ($P < 0.05$). At 1 year, worse survival was seen for older donors ($P < 0.05$) and for those with a prolonged cold ischemia time ($P =$ not significant). Improved survival was seen for donors with HBV/HCV/HTLV-positive serology, although this finding did not reach statistical significance. Finally, at 2 years, worse survival occurred only for older donors. Donors with positive serology continued to have significantly improved survival compared with standard donors.

Early Graft Loss (<90 Days Posttransplant)

Subgroup analysis was undertaken to determine those factors associated with early graft failure (Table 4). Three factors were found to be associated with early graft loss: increased donor age, low donor serum ALT, and recipient gender (female > male). Further analysis by recipient gender demonstrated that males received livers with a significantly lower median donor risk index (1.3 vs. 1.4, $P < 0.01$), which may account for the lower rate of early graft loss among this group.

ECD livers were not predisposed to a higher incidence of vascular complications (Table 5). The most frequent cause of graft loss using standard or ECD livers was intraoperative difficulties such as preexisting portal vein thrombosis, extensive previous upper abdominal surgery. The incidence of intraoperative issues leading to early graft loss was similar in both groups of recipients (Table 5). Sepsis due to bile leak or other causes was similar in both groups. PNF where the recipient died of poor liver function without serious identifiable contributing events was rare in our series. Only 1 case of true PNF occurred in the standard donor liver series. In this patient, the reason as to why this liver did not work was unclear. There were 4 cases of PNF in the recipients of ECD livers; and in contrast to the PNF case in the standard liver donor PNF, 3 of these cases can be attributed to faulty decision-making, or intraoperative problems. In 1 PNF, the donor was a 72-year-old whose liver had a 67-minute warm ischemia time and was put into a 71-year-old woman. The next case was a liver from a donor with a 46.5 BMI transplanted with a 60-minute warm ischemia time into a small woman with fulminant hepatic failure. The third PNF case was a 67-year-old donor liver that had a 17-hour cold ischemia time.

TABLE 3. Survival Analysis for Recipients of Both Standard (SD) and Extended Criteria Donors (ECD) With a Statistical Comparison of Each ECD Subgroup to the Standard Donor Group

	90-Day Graft/Patient Survival (n = 571)	*P** (SD vs. ECD)	1-Year Graft/Patient Survival (n = 442)	*P** (SD vs. ECD)	2-Year Graft/Patient Survival (n = 296)	*P** (SD vs. ECD)
Standard donors	91.3%/92.9%	Reference	84.0%/87.2%	Reference	77.6%/83.2%	Reference
ALL ECD donors	88.4%/89.7%	NS/NS	80.4%/81.5%	NS/NS	77.2%/78.8%	NS/NS
ECD criteria (*P* value for comparison of each ECD criteria versus SD)						
Age ≥60 yr	80.0%/80.0%	0.03/<0.01	67.4%/60.8%	0.03/0.01	61.5%/61.5%	0.13/0.03
BMI ≥35 kg/m^2	86.0%/88.0%	NS/NS	76.5%/82.4%	NS/NS	73.7%/78.9%	NS/NS
Serum Na ≥170	87.5%/87.5%	NS/NS	81.8%/81.8%	NS/NS	87.5%/87.5%	NS/NS
Elevated LFTs (AST/ALT >500 or TB >1.9)	88.0%/89.7%	NS/NS	81.4%/82.6%	NS/NS	74.5%/78.2%	NS/NS
High risk serology (HBV or HCV or HTLV)	96.4%/96.4%	NS/NS	93.0%/93.0%	NS/NS	92.6%/92.6%	NS/NS
More than 2 pressors	96.6%/98.3%	NS/NS	82.1%/82.1%	NS/NS	70.0%/70.0%	NS/NS
ICU stay >5 days	86.8%/88.7%	NS/NS	81.6%/81.6%	NS/NS	81.8%/81.8%	NS/NS
Extensive alcohol abuse	90.8%/90.8%	NS/NS	82.7%/82.7%	NS/NS	84.6%/84.6%	NS/NS
Cold ischemia time >12 hours	75.0%/75.0%	0.04/0.02	78.6%/78.6%	NS/NS	80.0%/80.0%	NS/NS

*Statistical comparison made using χ^2 test. Each of the ECD criteria subgroups are compared with the standard donor group.

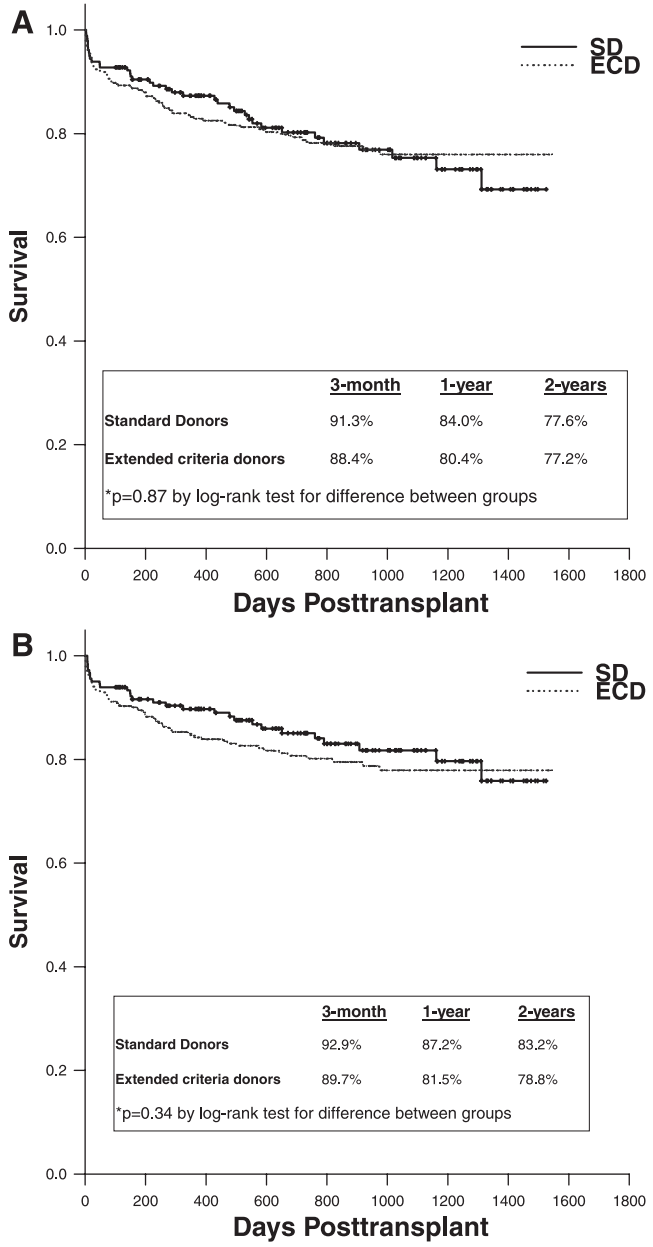

FIGURE 4. A, Overall liver transplant graft survival analysis: standard (SD) and extended criteria donors (ECD). B, Overall liver transplant patient survival analysis: standard (SD) and extended criteria donors (ECD).

TABLE 4. Comparison of Donor and Recipient Risk Factors for Early Graft Failure (<90 days posttransplant) After Liver Transplantation

	Early Graft Failure (n = 61)	No Early Graft Failure (n = 510)	P*
ECD	45/388 (11.6%)	343/388 (88.4%)	NS
Standard donors	16/183 (8.7%)	167/183 (91.3%)	
Donor factors*			
Donor age (yr)	45	41	<0.05
Donor BMI (kg/m^2)	26	25	NS
Serum Na (mEq/L)	154	156	NS
Serum AST (μL)	49	62	NS
Serum ALT (μL)	36	45	<0.05
Serum bilirubin (mg/dL)	0.8	0.8	NS
High risk serology	2/55 (3.6%)	53/55 (96.4%)	NS
Peak number of pressors	1	2	NS
ICU days	2	2	NS
EtOH abuse	6/65 (9.2%)	59/65 (90.8%)	NS
DCD	2/16 (12.5%)	14/16 (87.5%)	NS
Recipient factors*			
Age (yr)	51	52	NS
BMI	28	27	NS
MELD	19	16	NS
Recipient gender			0.03
Male	33/378 (8.7%)	345/378 (91.3%)	
Female	28/193 (14.5%)	165/193 (85.5%)	
Recipient race			NS
White	56/518 (10.8%)	462/518 (89.2%)	
Black	2/31 (6.5%)	29/31 (93.5%)	
Other	3/22 (13.6%)	19/22 (86.4%)	
Warm ischemia time	47 minutes	44 minutes	NS
Cold ischemia time (median)	8 hours	7 hours	NS

*Value is median where applicable. Comparisons made using median test and χ^2 test as appropriate.

ECD Utilization in High-Risk Recipients

A debate exists regarding who should receive ECD livers, those at the top of the list, or patients who have lower MELD scores and may be better able to withstand the physiologic challenge that a physiologically stressed graft may place on the recipient. We analyzed the graft and patient survival in 2 high-risk recipient groups: those with MELD score >25, and elderly recipients aged 59 and over.

Recipients with a MELD score 25 or > had worse graft survival at 3 months, 1 year, and 2 years when receiving an ECD liver rather than a standard liver donor (71.8, 56.3, and 56.5, vs. 90.0, 79.3, and 63.6 at 3 months, 1 year, and 2 years, $P < 0.05$ at 3 months and 1 year) (Fig. 5a). The patient survival was also worse among recipients with a MELD score 25 and higher that received an ECD liver when compared with those receiving a standard liver donor (74.4, 62.5, and 60.9 vs. 90.0, 82.8, and 68.2 at 3 months, 1 year, and 2 years, $P < 0.10$) (Fig. 5b).

Recipients age 59 and older receiving ECD livers had similar graft survival at 3 months, 1 year, and 2 years when compared with those receiving standard grafts (85.3%, 75.3%, and 76.9%, vs. 92.3%, 83.9%, and 71.4%, P = not significant) (Fig. 6a). Patient survival in recipients aged 59 and older receiving ECD livers was similar to that seen with recipients of standard grafts (88.1%, 79.0%, and 76.9%, vs. 92.3%, 83.9%, and 71.4%, P = not significant) (Fig. 6b).

DISCUSSION

The increasing disparity between the demand for and availability of suitable donor livers for transplantation re-

TABLE 5. Causes of Graft Loss Less Than 90 Days Posttransplant for Standard and Extended Criteria Donors

Cause of Graft Loss	Standard Donors (n = 183) [no. (%)]	Extended Criteria Donors (n = 388) [no. (%)]
Hepatic artery thrombosis	2 (1.1)	3 (0.8)
Portal vein thrombosis	1 (0.5)	1 (0.3)
Primary nonfunction	1 (0.5)	4 (1.0)
Bile leak with sepsis	2 (1.1)	3 (0.8)
Sepsis: other etiology	4 (2.2)	6 (1.5)
Recipient operative issue	4 (2.2)	11 (2.8)
Hyperacute rejection	0 (0)	2 (0.5)
Cardiac issues/MI	0 (0)	5 (1.3)
Preoperative liver failure: postoperative progression	1 (0.5)	2 (0.5)
Recurrent cancer	1 (0.5)	1 (0.3)
Recurrent HCV	0 (0)	1 (0.3)
Diabetic ketoacidosis	0 (0)	1 (0.3)

No differences reach statistical significance.

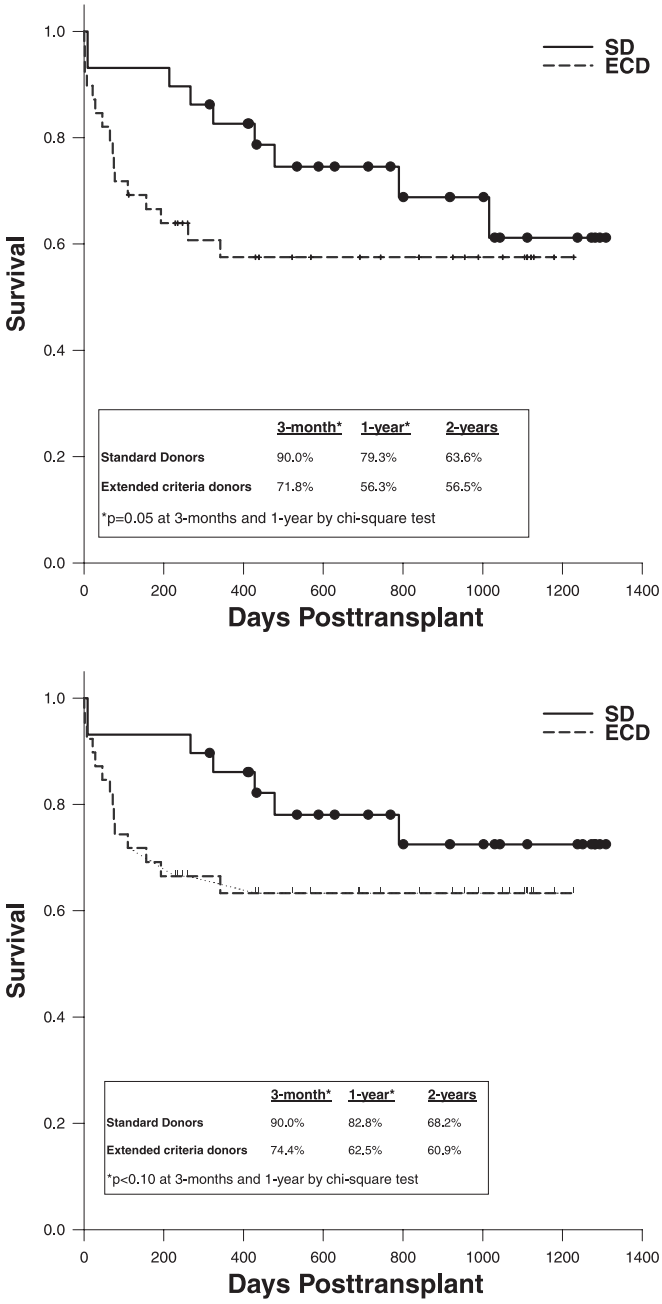

FIGURE 5. A, Liver transplant graft survival analysis: standard (SD) and extended criteria donors (ECD) in transplant recipients with MELD score 25 and higher. B, Liver transplant patient survival analysis: standard (SD) and extended criteria donors (ECD) in transplant recipients with MELD score 25 and higher.

quires drastic measures to lessen the severity of the shortage. Expansion of the donor pool through liberalization of acceptance criteria represents a readily available way to increase the number of donor livers available for transplantation. Our results demonstrate that systematic liberalization of acceptance criteria has a dramatic impact on the ability to transplant a greater percentage of the listed patients while decreasing those that die on the waiting list or are removed because they are too sick to transplant. Our results show that the use of ECD livers has not resulted in decreased graft or patient survival posttransplant. The increase in transplants that result from the routine use of ECD livers allows our program to transplant patients at lower MELD scores (ie, <25) prior to the onset of debilitating complications of liver disease.

The first step in the utilization of ECD livers is to identify those livers that result in inferior survival as a result of poor function, or disease transmission to the recipient. The classification of a donor liver as standard versus extended criteria should be based upon recently acquired data that reflects the current state of the art in liver transplantation. The liver transplant literature is filled with loose guidelines differentiating standard donors from ECDs.[6,8] Many of the rules of liver utilization were written in the late 1980s and early 1990s at a time when most liver transplant programs were just learning the nuances of the operative procedure and postoperative care.[14,15] The most dreaded complication in liver transplantation is PNF, which results in death if the recipient is not retransplanted quickly. True PNF, graft failure in the absence of other identifiable causes, was a rare event in our series (5 of 571). PNF is usually the result of recipient based intraoperative misadventures, poor decision-making, or technical/vascular complications.

Two broad categories of ECD livers exist; one is associated with risk for poor function based on physiologic stress or liver injury in the donor, and the other category is the risk of disease transmission from donor to recipient. The first broad class of ECD livers is the group at risk for parenchymal injury. These grafts need to be evaluated carefully and transplanted into recipients that are able to withstand the increased physiologic stress that may be placed on them. Our results have shown livers with cold ischemic times greater than 12 hours, and livers from donors 60 years and older; result in

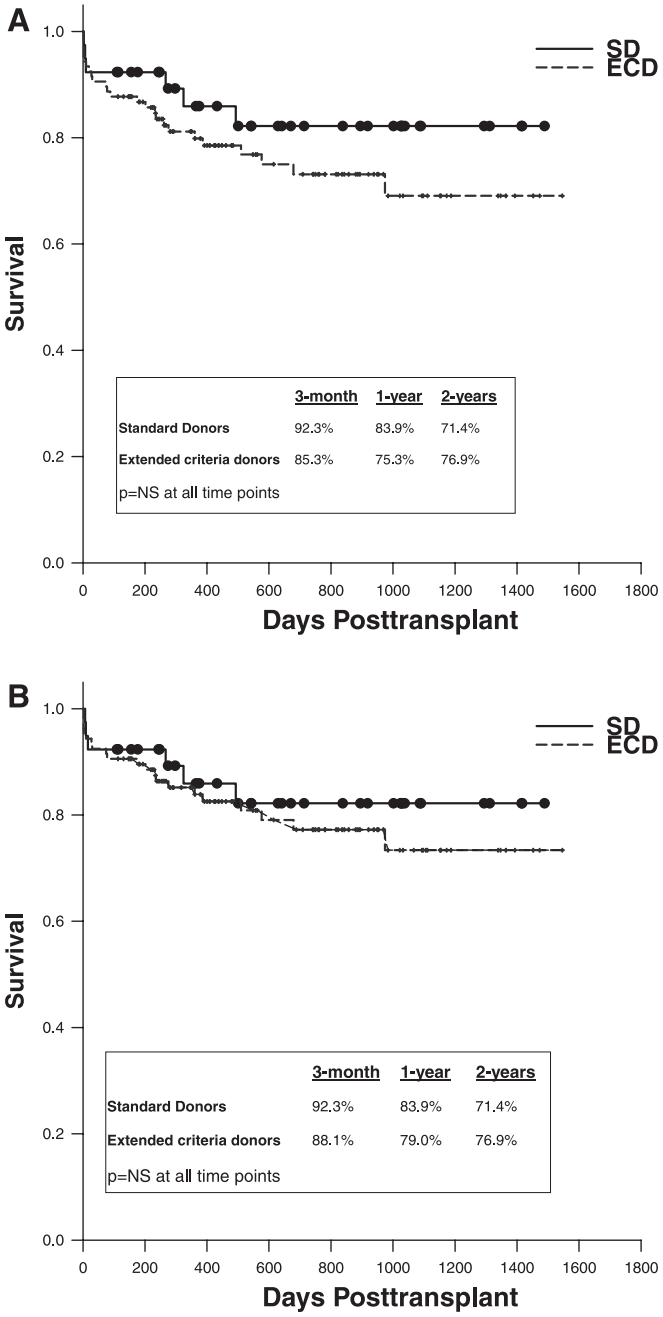

FIGURE 6. A, Liver transplant graft survival analysis: standard (SD) and extended criteria donors (ECD) among transplant recipients age 59 and older. B, Liver transplant patient survival analysis: standard (SD) and extended criteria donors (ECD) among transplant recipients age 59 and older.

inferior graft and patient survival, justifying classification as ECD livers. These results are consistent with other large series that identify age and prolonged cold ischemia as significant risk factors for early graft failure.[16] It should be possible to decrease the number of livers with cold ischemia time greater than 12 hours by improving operating room efficiency, and starting transplants as soon as the donor liver arrives at the transplant center. There will always be cases where there is a recipient problem and a donor liver accrues more than 12 hours of cold ischemia. Livers with cold ischemia times greater than 12 hours should in general be restricted to younger donors with no other risk factors for increased physiologic stress. Donor livers with cold ischemia times greater than 12 hours place significant stress on the recipient cardiovascular system, and so these grafts should be directed toward younger recipients. Grafts with prolonged ischemia should specifically be directed away from frail older recipients with cardiac issues.

Results with grafts from donors 60 and older were inferior with regards to graft and patient survival. There were only 60 such grafts in our series and 12 of these failed within 90 days posttransplant. None of these 12 early failures was the result of PNF or poor graft function (data not shown). Instead, the cases were plagued by poor decisions regarding recipient selection, intraoperative technical complications, and standard postoperative complications (sepsis, myocardial infarction). It is quite possible that the fact that livers from donors greater than 60 years of age meet ECD designation in our series is a direct result of our decision-making, and not a reflection of their graft quality. There are ample data from other large databases to suggest that older donor livers are inferior to younger donor livers.[11,17] It is unclear if other centers may have placed older donor livers at a distinct disadvantage with recipient selection issues, as was the case with our series.

The ECD liver disease transmission risk is broken into 2 separate categories, the first being viral transmission of HCV, HBV, HTLV-1, and HTLV-2. The second category is the risk of transmitting malignancy from donor to recipient. The most common viral scenario is that of the HCV positive donor. Our results are in keeping with other large series that suggest that it is safe to put HCV positive donor livers into recipients with HCV.[18–21] Our program places HCV-positive donor livers into recipients with HCV genotype 1 only. The HCV positive donor liver must have no evidence of cirrhosis or stage 2 fibrosis. Over time, we have placed less emphasis on the degree of inflammation in frozen biopsy specimens. Our results clearly suggest that HCV-positive donor livers may in fact be preferred grafts for the recipient with HCV genotype 1-induced liver disease. It is clear that HCV-positive livers should be declassified as ECDs. HBV disease risk has been examined by many centers, and it is clear that it is safe to use HBcAb-positive donors and then place the recipient on lifelong antiviral therapy. Some debate exists regarding who should receive HBcAb-positive donors, but it seems, in light of the current donor shortage, that the restrictions on who should receive such a graft should be minimal.[19,22,23] Little is known regarding the risk of transmission of HTLV-1 and -2. Initial reports using these organs are promising and have been reinforced by our series of patients.[24] HTLV-1 and -2-positive donors will require close long-term monitoring to determine if there is indeed substantial risk of disease transmission.

The second sizeable group of donors with increased risk for disease transmission is those with a history of previous malignancy. In our series of donor livers with malignancy, no transmission of donor cancer has occurred thus far. The Penn

Tumor Registry has ample documentation that cancer transmission does indeed occur, but the transplant community needs to determine what is an acceptable transmission rate.[25–27] If the transmission rate is low, then the opportunity to benefit the majority of the recipients of donor livers from patients with malignancy might be worth the increased risk in light of the worsening shortage of donor livers.

Declassification of ECD livers that provide graft and patient survival equivalent to standard donor livers will be important to minimize wastage of useable livers. Our series shows that livers from donors with Na+ >170, BMI >35, significantly elevated liver chemistries, and extensive ethanol abuse should be declassified as ECDs. Elevated donor sodium (Na+ >155) has been identified as a major risk for PNF and initial poor function. These grafts may be physiologically stressed, but most of the data that identified elevated serum sodium in the donor as a risk for PNF were generated in the late 1980s and 1990s.[13] The results of our series clearly show that the risk for PNF and early graft loss is not elevated. The reason why high donor sodium was not an increased risk in our series is unclear, but it is possible that improvements in surgical technique and ICU management could play a role in the difference.

It will be important to define which patients should not receive an ECD liver if at all possible. Our results clearly show that recipients with MELD scores 25 or greater tolerate ECD livers poorly. Large reported series have shown a similar decline in survival when using marginal livers in sick patients.[16] If ECD livers are to be used in the higher-MELD candidates, the recipients should be younger and free from extensive abdominal surgery and cardiac issues (data not shown). Elderly recipients of ECD livers did not fare differently than those that received standard donors, which may have been the result of careful donor/recipient matching. These results are similar to those from other published series.[28] It is clear from our results that ECD livers can be used in the elderly recipient.

Our results suggest that significant room for expansion of criteria for acceptable liver donors exists. We place great importance on minimization of stress on physiologically compromised liver grafts. We do 3 things perioperatively to minimize the stress of transplantation: 1) minimize the cold ischemic time, 2) use the piggyback to decrease the warm ischemic time, and 3) delay fascia closure to decrease abdominal compartment pressure on the liver. Warm ischemic time greater than 45 minutes is a significant risk factor for graft failure.[29] In 2003 to 2005, our median warm ischemic time dropped from 43 to 27 minutes (data not shown). Programs using significant numbers of ECD livers should consider using the piggyback technique for all cases to minimize warm ischemic time.[30] Our program places great emphasis on delayed fascial closure to minimize abdominal compartment pressure on the new liver. The detrimental effects of compartment pressures on abdominal organ perfusion have been well documented in trauma but are less well studied in liver transplantation.[31]

There are 2 points that must be addressed before widespread application of liberalization of donor acceptance criteria can occur. The use of the MELD score for liver allocation, which is an accurate predictor of pretransplant death but not posttransplant survival, will direct ECD organs toward high-risk recipients. Our results are consistent with other series that show that recipients with high MELD scores will derive the least benefit from the ECD strategy.[16] It will be important to develop ways to consider both disease severity (MELD score) and posttransplant survival in organ allocation in the future. The second point is that minimum standards for acceptable posttransplant survival need to be defined.

CONCLUSION

Liver grafts from extended criteria donors (ECDs) can be used to drastically reduce wait list time with outcomes comparable to those for standard donors. Of the multiple ECD criteria examined, only donor age >60 years and cold ischemia time >12 hours resulted in reduced graft and patient survival. As experience using ECD livers increases, the results should be analyzed so that donor boundaries will be in a constant state of reassessment.

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DISCUSSIONS

DR. RONALD W. BUSUTTIL (LOS ANGELES, CALIFORNIA): I think congratulations are due to Dr. Tector and his colleagues for both the paper presented here and the work that they have done at Indiana University; namely, reducing the center's wait list from 257 patients down to only 30. This is indeed an impressive accomplishment. And now the median waiting time is only 18 days, which is probably one of the best in the country.

The authors report this accomplishment was made possible by the aggressive use of extended criteria donor grafts. In fact, the utilization of suboptimal donors is no longer controversial in the field of liver transplantation and has been well reported for many years. UNOS reports that in 1990 only 10% of donors were over the age of 50, but by 2003 that percentage was over 35% of all donors. Clearly, Dr. Tector, ECDs, or extended criteria donors, have arrived, are here to stay, and have been the most effective way in expanding the limited donor pool. However, as the authors correctly point out, a rigorous definition of the "extended criteria" donor remains elusive. And this leads to my first question.

Might the authors have been too liberal in their criteria for determining which donors showed "extended criteria?" Some of the criteria they selected, such as HLTV positivity, history of cancer, or the history of alcoholism, do indeed describe a suboptimal donor but might be expected to impact long-term outcomes as opposed to early results with PMF, or primary nonfunction, or delayed graft function as has been typically the concern of marginal donors. With these liberal criteria the authors report that 68% of their donors were extended criteria, which is a high number even for a very aggressive center. Have you done an analysis to determine which indeed of these factors are the most predictive of an extended criteria donor and would impact on graft and patient survival?

The authors saw no effect of an elevated peak sodium in their extended criteria donors, and we have recently had a similar experience at UCLA. To what do they a tribute this phenomenon when other centers reported this is a predictor of poor outcome? Do the authors or their local OPO manage their donors in a specific fashion to abrogate the effects of a high sodium?

The authors report that the average MELD of their recipients in this series was 17. Do they think that this relatively low value may have obscured the deleterious effects of these grafts which might have been seen with a higher MELD score? In fact, your subgroup analysis shows that these grafts in patients with a MELD greater than 25 don't do as well, which we would certainly agree with.

Finally, perhaps the most difficult question, based on these data, do you think that there should be some consideration of a tweaking of the organ allocation system to allow these extended criteria donors to be placed in more appropriate recipients rather than putting them into the most sick recipients as is currently the case?

DR. A. JOSEPH TECTOR, III (INDIANAPOLIS, INDIANA): As far as did we determine the factors that were more predictive, the answer is we have not. I don't think we are remotely ready to say what makes a graft not work. We were absolutely too liberal in our definition of extended criteria grafts. But you, as well as anybody here, know from being up on the phone at night that the categories that we are using as ECD are reasons that you are getting offered a lot of these livers, so that you may be using all of these.

But the point is there are a lot of people that are not using these organs. So I think that clearly there is a lot of room for us to increase liver utilization. And the important thing is going to be to define which livers should be declassified as ECD. I will tell you that certainly the HCV-positive donors should be removed, high-sodium BMI. I would think most of the things we that talked about should be declassified as extended criteria donors so that we do not analyze these livers as ECD and actually make it harder for us to be able to use these grafts.

The one thing that I can tell you we are very afraid of, and this is more of a practical point, is the donor that can't

maintain a normal pH, that has a bad pH with a low bicarb. That makes us very afraid. And that is really the only thing that turns us off.

As far as the peak sodium goes, I have no explanation for it. The only thing I can tell you is that I could never in my own mind draw a picture of why a high sodium would make the liver not work. So we don't use high sodium. I don't know what the sodium is when I evaluate a donor. We don't manage the donor specifically to drop the sodium.

As far as the lower MELD scores, I think that one of the things is by liberalizing your acceptance criteria; and what you have hit on, the important point, is using the MELD score as the sole mode of allocation, you specifically put these livers into the patients that have the worst chance of benefiting from them. So I think it is going to be critical, as we move forward, that there is some wiggle room for the surgeon to have some ability to decide who is the right patient for some of these organs to achieve maximal benefit.

I personally think that there are good data to say to transplant very low MELD scores that those patients are harmed rather than helped by a liver transplant. If I had to guess, I would think that probably transplanting between 10 and 25 is probably the ideal that we should all strive for as a country. So I think that if you get to a point where you can clean off the list from the middle, the people over 25 will either get transplanted quickly or die off. And that is what has happened in our program.

Dr. Goran B. Klintmalm (Dallas, Texas): Thank you so much for leading us into this discussion because I think it adds tremendously to what you just presented. The term "extended criteria donor" has become a very popular phrase in recent years. It is common to claim extensive use of ECD donors as proof of the aggressiveness of one's program.

There is, however, a down side. Patients and their lawyers read such papers to find reasons to why their transplant was not successful or why the patient should have been warned and specially considered, and then to sue the surgeons.

In my experience with almost 3000 liver transplants, each and every one of the criteria mentioned in this paper we considered as normal findings except HCV positivity and ECD donors, even when these other factors were found together. The finding that the ECD criterion applies to 68% of your transplants suggests a substantially different criterion should have been used. That is to say, the criterion you used does not describe extended criteria donors, but normal donors.

My question is—and I have 2—would it have been better to look at the 10% most advanced donors to see what they represent and what impact they have? Number 2, the correct conclusion of this paper is that you have used too narrow criteria in the past. And I think you actually alluded to that in your discussion previously.

Dr. A. Joseph Tector, III (Indianapolis, Indiana): I would agree 100% that the criteria are far too narrow. In all honesty, we wanted to use liberalization of acceptance criteria. It didn't fit in the abstract title. So we went to the ECD because it at least was able to get us so that we could use the data. But I agree that it has been way too narrow a definition as far as what is an acceptable donor.

As far as the legality, I think that is very important. In our center, we are extremely careful to never use that term. In fact, I think people have probably heard this from me before, we tell all the patients Cinderella and Snow White are dead, you will not be getting their livers, and if you need to know a great deal about your donor, you probably will have to wait a little bit longer until we can find somebody that will meet up to your standards. So I agree with everything you have said.

Dr. Robert M. Merion (Ann Arbor, Michigan): I think we have now established through the discussion that there is no way really to define ECD liver. It is not an all-or-none or a black-and-white situation. There is a spectrum of donor quality and that is going to be associated with a spectrum of outcome.

You may be aware that there was an ECD Liver Symposium that was held last year. At that symposium, based on work done with our group, in collaboration with Sandy Feng at UCSF, we developed the concept of a continuous donor risk index, which would take into account observable and quantifiable issues that might impact on recipient outcome. We looked at donor age, cause of death, donor race, donation after cardiac death (DCD), and so on, combining them mathematically into a donor risk index. And using that, if one looks nationally, what we put out there as what we think is the increasingly elusive ideal donor; in fact, the relative risk of the average donor being used in the United States is about 1.2 compared to the Cinderella or Snow White donor that you alluded to; and only 12% have a risk of failure that is even as high as the DCD donor that I described in my talk yesterday.

So while we talk a lot about using high-risk donors, in fact, we actually are not using donors that can be demonstrated to have that high of a risk of failure. We will be presenting data at the ILTS meeting in Milan in a couple of weeks showing that if you use donors that have a high risk of failure in low or even medium MELD recipients, that they actually have a worse survival with a transplant than they would have had if they not received a transplant at all. That leads me to 3 questions.

First, given that it has been described that patients who have a MELD score below 15 do not have a survival benefit from a transplant even using an average donor, how do you justify using high-risk donors for 50% of your patients who have a MELD score of 16 or lower?

Second, among those patients who do have a high MELD score, I wonder if you might speculate on any potential strategies that might be able to be used to ameliorate the risk that you did show in some of your subgroup analyses.

Third, could you outline for us what process you used for informing your potential recipients about the nature of the

risk that you believe that they are undertaking when they go forward with a transplant?

Dr. A. Joseph Tector, III (Indianapolis, Indiana): With regards to transplanting people with the lower MELD and the risk, as far as that goes, the people on the low, low end of the MELD usually have some other extenuating circumstance. We didn't bring people in that had MELD scores of 6 that were working and feeling well. A lot of these people had tumors, cholangiocarcinomas, or had some other very debilitating problem, and I think there are a lot of people that fall outside the cracks with the MELD score that don't get service. So I think that is an important consideration that moving forward as a field we are going to have to figure out.

As far as ameliorating the risk, I would tell you: we looked at the donor. As soon as you put out the donor risk index—in the manuscript, and we actually put all of our cases in the donor risk index. And we have been having a hard time to know exactly what to say about the data.

What I can tell you is you place a lot of emphasis on cold ischemic time. I know that that is a risk. I think that it is a risk that can be minimized. And I would just say to be rewarded donor risk index-wise because you had a graft that went in at 12 or 14 or 15 hours; our median cold ischemic time is 7 hours. And as you saw in our series, we only used 20 of the 570 grafts, which were put in after 12 hours. And most of those were situational problems, some other center was going to do the transplant and something happened to the recipient. So I think the cold ischemic time is something that should be factored in, but I don't think it should be rewarded. I think we should all push to minimize cold ischemic time.

As far as informed consent, I think it is very hard to inform somebody when you don't really know what the risks are. The big issue for me is: I wouldn't put a graft in that I didn't think was going to work. When people have very low MELD scores, such as cholangiocarcinomas, tumors that are outside—get no exception points. They ask, "How am I going to get a liver with such a low MELD score?" Then you have to sit down and say we are going to have to use a liver from somebody that isn't going to be accepted by a lot of centers and that is associated with an increased risk of graft failure and death. But they have no other option, and they usually go for it.

Dr. Henri Bismuth (Villejuif, France): I agree with you for the extended criteria donor. My remark is on the split liver that you exclude too easily. Of course, it needs surgical expertise. Without expertise, it is a problem but with expertise it is a solution. So you have to preach also for the use of split liver. It is not the same graft; it is exactly the opposite. You use the bad graft, and for the split, we use only the good graft. As you said and already said by many others, the pool of the liver grafts may be increased by about 30%. There is no competition between the 2 grafts and it is a pity not to use split liver.

Dr. A. Joseph Tector, III (Indianapolis, Indiana): I would agree with you. You are a master surgeon, and I think everyone here would recognize to that. But I think as a global means to improve the shortage of organs, I think liberalizing your acceptance criteria is probably an easier way that more programs can get in the game faster. But I think that you are absolutely right about the split liver being a great tool.

Dr. Nancy L. Ascher (San Francisco, California): Echoing what Dr. Bismuth said, I would not discount the live donor liver graft as a source for more donors. I think you have to recognize it took 48 years between the first successful live donor kidney transplant and the point in time where live donors exceeded cadaveric donors. So again it is another alternative.

I have 2 questions. You made the comment you wouldn't put a graft in that you didn't think was going to work. In fact, the early NIH Liver Transplant Database indicated that the subjective observation by the surgeon of the liver was actually more predictive than any of the objective criteria that we used. You obviously put these grafts in, so the surgeon thought all these grafts were going to work. Do you have any data on the surgeons' impression of the graft? Second, you alluded to some issues in the recipient operation that caused the loss of quite a few grafts. I wonder if you would elaborate on these issues.

Dr. A. Joseph Tector, III (Indianapolis, Indiana): I am not sure what you mean by do I have data on the surgeon.

Dr. Nancy L. Ascher (San Francisco, California): The original database determined that the donor surgeon's subject of assessment of the liver was more important than any of the objective factors that we were measuring at that time. Do you have any of that subjective, the donor surgeon said, "Yes, this graft will work"? Or I assume the donor surgeons said all these grafts will work, no round edges, no didn't flush well. Do you have any of that data?

Dr. A. Joseph Tector, III (Indianapolis, Indiana): No, we don't. We didn't keep that data. Can you give me the second question again?

Dr. Nancy L. Ascher (San Francisco, California): The fact there were recipient problems that caused the graft losses and that the graft losses were not due to donor factors. You said events in the recipient operation. Was this one long warm ischemic time? Exactly what was it?

Dr. A. Joseph Tector, III (Indianapolis, Indiana): If you look at the early graft loss, the warm ischemic time was significantly higher in the early graft loss group than in the recipients that did not have early graft loss. And warm ischemic time is often reflective of degree of difficulty of the operation. Sometimes you get in there and you find you have a completely clotted portal vein you didn't expect. Sometimes, you know, you have a lot of previous surgery and you just have a lot of difficulties, perioperative MIs. Those are the kinds of events we are talking about.